REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1, 2, 5-7, 9-14, 19-24 and 26-38 will be pending in the application subsequent to entry of this amendment.

Discussion of Added Claims

New dependent claims 36 to 38 have been added. New claims 36 and 37 specify that the pharmaceutical composition used must be water-soluble. Claim 36 is a composition claim dependent on claim 1 and claim 37 is a method claim dependent on claim 26. New claim 38 specifies that when the pharmaceutical composition is introduced into the intestines, the additive (c) enhances the solubility of the non-conjugated bile salt (b).

The section from page 1, line 20 to page 2, line 2 of the description explains the importance of solubility in the environment of the intestines (which is aqueous) and so provides basis for new claims 36 and 37. As for claim 38, it was explained in the application as filed e.g. at page 2 lines 11-13 and 28-32 that the additive in the present invention (PG or BHA) and non-conjugated bile salts mutually enhance each other's solubility in water. This provides support for new claim 38. No new subject matter has been added in these claims.

The objections raised in the Office Action are discussed in turn below.

Sections 1 to 10 – Obviousness

In the previous Office Action (mail date January 28, 2008) the Examiner alleged that it was obvious to replace the sodium bicarbonate used in the compositions of US 5,853,748 (hereafter '748) with propyl gallate (hereafter PG) or butyl hydroxy anisole (hereafter BHA). In section 1 of the present Office Action the Examiner kindly indicates that this previous objection has now been withdrawn. However, the Examiner now suggests that it would have been obvious to (i) add PG or BHA to the '748 composition (i.e. without removing sodium bicarbonate), and then (ii) reduce the pH of the composition to somewhere in the region of 6.8 to 7.5.

Regarding (i), it is respectfully submitted that the Examiner's objection is wrong because this step would result in an unworkable composition. It is important to note here that one of the important attributes of compositions of the present invention is that they enable the production of a clear solution in water. This was clearly set out in the application as filed at e.g. page 1, lines 6 to 9 and page 1, line 20 to page 2, line 2; as explained in these passages, a clear solution is more efficacious than a precipitate mixture. PG and BHA have the surprising effect of enhancing the

solubility of non-conjugated bile salts in water. This enables the preparation of clear aqueous solutions containing non-conjugated bile acids or salts without having to raise the pH, thereby avoiding both the disadvantages of having a higher pH in the intestines (e.g. enhanced protease activity) and adverse effects caused by the pH-raising agent (e.g. effects on the integrity of sensitive macromolecular active principles).

As is evident from the results described in the attached Declaration of Dr. New, incorporating both sodium bicarbonate and PG or BHA in the same mixture (along with a non-conjugated bile acid or salt) creates a turbid dispersion, regardless of whether the PG/BHA or sodium bicarbonate is added first. In other words, the resulting composition is not suitable for use according to the present invention.

Accordingly, step (i), which the Examiner suggests would have been obvious to the skilled person, would in fact not have been obvious at all. The skilled person would clearly have been concerned with incompatibilities between PG/BHA and sodium bicarbonate in terms of solubility; one is an organic aromatic alcohol that is known to be hydrophobic, the other is an inorganic ionic compound. The results reported in the attached Declaration confirm that the skilled person's fears would have been well founded and indeed would have been realized.

Moreover, compositions rendered unworkable by the addition of an incompatible additive such as sodium bicarbonate are clearly not envisaged in the present application. Thus, even if the skilled person had attempted to combine sodium bicarbonate and PG/BHA in the same composition, this would not have led to claim 1.

Further, as has been explained in previous submissions and proven by the extracts from the Handbook of Pharmaceutical of Excipients that have been filed, both PG and BHA have very poor solubility in water. It is for this reason that their main use is in preventing rancidity in oils and fats. Thus, it is not credible to suggest that a skilled person would have thought to use them in compositions which are destined to be released in an aqueous environment, especially when the aim of the compositions is to achieve a concentrated but clear and proper aqueous solution of the components.

Apart from the fact that PG and BHA would not have been considered outright due to their known hydrophobicity, there are a host other known antioxidants that the skilled person would have been far more likely to consider. For instance, vitamin C, sodium metabisulphite or

malic acid (all of which are GRAS-listed) would have been obvious candidates due to their known hydrophilicity. Notwithstanding that, as has also already been explained in previous submissions, when PG or BHA are used as antioxidants, as a general rule they are used only at very low concentrations, e.g. in WO 02/22158 they are used at a concentration of 0.0008 - 0.0009%. It is generally considered that higher concentrations of the compounds give no added antioxidant benefit, and it is thus standard pharmaceutical practice to restrict the concentration of the antioxidants in formulations to at most 0.1 %, typically much less than that.

Accordingly, if (as postulated by the Examiner) the skilled person had been motivated to preserve the formulation and prevent degradation, he would surely have added a hydrophilic antioxidant such as vitamin C, in a low concentration. This would have led away from claim 1. Any suggestion that a skilled person would have added BHA or PG to the '748 composition can only be made with the benefit of hindsight, which is of course not permitted when assessing obviousness.

Regarding (ii), the Examiner suggests that the skilled person would have thought it obvious to lower the pH of the sodium bicarbonate-containing composition (after adding PG or BHA). However, there is no suggestion as to how this might be done. The '748 compositions have sodium bicarbonate specifically incorporated in them in order to buffer the pH of the environment to 7.5 to 9 when the composition is released in the gut. Sodium bicarbonate is an effective buffer at a high pH, with two pKas of 6.4 and 10.3. Solutions with sodium bicarbonate naturally achieve a pH of 8 to 8.5. To lower the pH from this range would require the addition of such large amounts of other agents that the formulation would be unfeasible.

Moreover, as has been said before, lowering the pH of the '748 compositions would be completely at odds with the document's teaching. The whole point of the '748 compositions is that they bring about and maintain a high pH in the intestinal environment once they are released there, in order to enhance the bile salt solubility. Lowering the pH would therefore defeat the objection of the exercise. Thus, the skilled person would not have considered lowering the pH for fear of prejudicing the activity of the compositions.

On a different note, reference is made to the third paragraph on page 10 of the Office Action. Here, the Examiner notes that claim 1 does not recite that the PG or BHA enhances the solubility of the bile salt. However, there is no need to recite this in the claim. It is a matter of

empirical fact that PG and BHA do enhance bile salt solubility in the aqueous environment of the intestines. This was illustrated in the Examples of the application as filed, see e.g. Examples 3 and 4.

As a final comment on obviousness, reference is made to the recent decision of The Supreme Court in the case of KSR v. Teleflex. The Supreme Court's opinion states that an obviousness enquiry "must ask whether the improvement [represented in the claimed invention] is more than the predictable use of prior art elements according to their established functions". It is respectfully submitted that the present Examiner has not done this. As has been explained previously, the ability of PG and BHA to enhance the solubility of non-conjugated bile salts in the intestines is entirely unexpected and there is not even a suggestion anywhere in the prior art pointing towards this ability. Thus, the invention underlying the claimed compositions and methods is clearly an improvement that is more than the predictable use of prior art elements according to their established functions. This is a further reason why the claimed compositions and methods are not obvious from the prior art.

Sections 11 to 15 – Indefiniteness

Firstly, the Examiner asserts that the expression "does not raise the pH of the intestinal fluid above pH 7.5" in claim 1 is unclear because no lower limit is given. With respect, the applicant disagrees. It is believed that a person of skill in the art would have no difficulty understanding whether or not this criterion was met by a given composition and would not be concerned with the lack of a lower limit: quite simply, if the composition raises the pH above 7.5 it is excluded from the claim, but if it does not then it may be covered.

Secondly, the Examiner objects that the references to "derivatives and analogues, either synthetic or from natural sources, conforming to structures derived from either human or animal origin [of insulin, etc]" in claims 9 to 11 and 19 to 21 are unclear. With respect, the applicant disagrees: it is submitted that a person of skill in the art would not have difficulty understanding what the terms in question mean.

Consider, for instance, the case of insulin. Plainly, a compound that might be considered to be a derivative of insulin in chemical terms but is in reality completely inactive is not covered by the claims of the present application. The claims refer to an "active macromolecular principle" and claim 1 requires the composition to be a pharmaceutical composition. Thus, a

skilled person would appreciate that the derivatives and analogues of insulin according to claims 9-11 and 19-21 are simply those that work. The active derivatives and analogues of insulin are both well known and a matter of public record, being described in standard pharmaceutical drug listings/encyclopedias. By way of example, the Examiner's attention is directed to the accompanying extract from the thirteenth edition of the Merck Index. Various well-known derivatives and analogues of insulin are listed. Aside from human insulin there are non-human insulin analogues (e.g. bovine or porcine insulin), derivatives of insulin (e.g. zinc insulin) and synthetic analogues of insulin (e.g. insulin aspart, which is produced by recombinant DNA technology).

The present invention is generally applicable to all macromolecules. To describe each and every analogue and derivative of every possible macromolecule (along with details of how to use each one) would require a significant portion of the Merck Index to be reproduced in the specification. That is not only unnecessary but also highly undesirable. All it would achieve is the proliferation of a vast amount of information that is already both known and readily available to those of skill in the art. Instead, it is clearly appropriate simply to indicate that, although the present invention works well with insulin, there is no difficulty in using a derivative or analogue of insulin instead. Moreover, given the different types of derivative and analogue of insulin that exist, for the sake of clarity it helps to make explicit in the claim that both synthetic and natural variations are covered, and that they can conform to structures derived from either human or animal origin. That is what has been done in claims 9-11 and 19-21, and the skilled person would have no difficulty understanding it.

Similar considerations apply to the other macromolecules listed in claims 9-11 and 19-21. Accordingly, the phrase to which the Examiner has objected is respectfully maintained.

Sections 11 to 15 – Written Description

The Examiner objects that the phrase "derivatives and analogues, either... ...origin" discussed in the preceding section contravene the written description requirement. The applicant also respectfully contests this objection.

The Examiner refers to the case of *Regents of the University of California v. Eli Lilly & Co.* The section quoted from this case includes a reference to some earlier case law, namely *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973), which is quoted as

follows: "In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus" (emphasis added). Subsequently, on page 16, the Examiner states "If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus." (emphasis added).

It is believed that in the present case the applicant has clearly demonstrated sufficient variety in the identity of the macromolecule. Thus, the application as filed included details of experiments conducted with two very different macromolecules, namely insulin and calcitonin, and both were shown to work, i.e. the addition of additive (c) as defined in claim 1 enhanced the solubility of the bile salt (*see* Examples 3 and 4), and in turn this enhanced the absorption of the macromolecule (*see* Examples 6 and 7).

Insulin and calcitonin have no homology whatsoever. To name but a few differences, they possess completely different sequences, tertiary structures, isoelectric points and molecular weights. The exemplification of these two macromolecules clearly overcomes any suggestion that the efficacy of the invention is related to any particular chemical characteristic that limits the invention to just one particular subset of macromolecules. Given that success has been proven for two such different macromolecules, the skilled person would have no difficulty appreciating that the invention would work with e.g. derivatives and analogues of insulin as well as it does with insulin. In other words, to use the wording from the case of *Regents of the University of California v. Eli Lilly & Co.*, the skilled person would not consider there is any unpredictability in performance in connection with analogues and derivatives of insulin.

Finally, it is worth noting that earlier in prosecution the Examiner explicitly stated "The use of bile salts to enhance the permeability of macromolecular drugs is well-known in the prior art (*see* for example New, U.S. Patent No. 5,853,748)" at page 4, section 13 of the Office Action with a mail date of February 1, 2007. The compositions of the present invention achieve success, namely the enhancement of uptake of macromolecules, by increasing the solubility and therefore availability of non-conjugated bile salts in the intestinal environment. The ability of PG and BHA to do this is proven in Examples 3 and 4 of the present application. The result of this effect (*see* e.g. Examples 6 and 7) is that the already known ability of such bile salts to

enhance the permeability of macromolecular drugs is enhanced. Given that the USPTO Examiner already stated that bile salts enhance the permeability of all types of macromolecules, it cannot now be argued by the present Examiner that there is any doubt over whether the bile salts used in the present invention would enhance the permeability of different analogues and derivatives of e.g. insulin.

Similar considerations apply to the other macromolecules listed in claims 9-11 and 19-21 as do to insulin. Accordingly, it is submitted that the objection raised in connection with the written description requirement should be withdrawn.

Favorable reconsideration of this application is respectfully requested. Should the examiner require further information please contact the undersigned.

Respectfully submitted,

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